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ORIGINAL RESEARCH ARTICLE

Economic Analysis and Budget Impact of Tenofovir and Entecavir in the First-Line Treatment of Hepatitis B Virus in Italy

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Abstract

Background Chronic hepatitis B is a common, progressive disease, particularly when viral replication is detected. Oral antivirals can suppress viral replication and prevent or delay the development of cirrhosis and liver-related complications. The treatments of chronic hepatitis B cannot totally cure the disease but can prevent its progression to hepatocellular carcinoma, decreasing the levels of both morbidity and mortality. To date, there are several therapies indicated by the international guidelines as first-line treatments for the management of hepatitis B; two of the most effective are those based on either tenofovir or entecavir.

Objective The aim of this study is to evaluate the cost-effectiveness of tenofovir and entecavir in the treatment of naïve patients with chronic hepatitis B. The two treatments are compared with the "no treatment" and to one another.

Methods The cost-effectiveness analysis was conducted using a Markov model; patients entered one of the following health states: chronic hepatitis, cirrhosis (compensated or decompensated), hepatocellular carcinoma, liver transplantation or death. The analysis was carried out from the perspective of the Italian National Health Service by considering a life-time horizon with cycles lasting 1 year and with costs and QALYs (quality-adjusted life years) discounted at a rate of 3.5%. The results of the model were analysed in terms of incremental cost-effectiveness ratio (ICER).

Results ICERs for tenofovir and entecavir emerging from the comparison versus "no treatment" were equal to €10,274.73 and €16,300.44 per QALY gained, respectively, on the life-time horizon. Tenofovir was dominant in the direct comparison with entecavir, indicating more QALYs and a lower consumption of resources. The Monte Carlo simulation demonstrated that in 97% (tenofovir) and in 85% (entecavir) of the scenarios performed, the cost per QALY fell below the threshold of €30,000/QALY. The budget impact analysis showed savings for tenofovir amounting to 33% compared to entecavir in the first year on treatment and to 31% in following years.

Conclusions Entecavir and tenofovir are recommended for the treatment of patients with chronic Hepatitis B in the Italian Health System. In particular, tenofovir appeared to be the more cost-effective drug for the management of chronic hepatitis B virus (HBV) infections. These results could help decision makers and clinicians to address their decision when choosing a first-line treatment for the management of people affected by chronic HBV.

Key Points for Decision Makers

Both tenofovir and entecavir appear cost effective compared with no therapy for the treatment of chronic hepatitis B in Italy.

Tenofovir allows to achieve a higher level of QALYs than entecavir (4.89 vs. 4.85), with a positive differential equal to 0.04 QALYs.

Tenofovir is associated with estimated cost savings of 33% as compared to entecavir at the end of the first year from its introduction in Italy (€66,507,763 vs. €99,805,085).

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1 Introduction

Hepatitis B is a form of viral hepatitis caused by an infectious agent called hepatitis B virus (HBV) [1]. The HBV is a major cause of liver failure and liver cancer. Typically, a HBV carrier has no signs or symptoms of infection and can unknowingly transmit the virus for years. It is possible to distinguish between:

- acute hepatitis B infection, which lasts less than 6 months; the immune system is usually able to successfully fight the virus [2];
- chronic hepatitis B, which lasts more than 6 months: when the immune system is unable to fight the virus, the infection can become permanent and lead to serious complications (cirrhosis and liver cancer). Most infants infected by HBV at birth and many children infected before 5 years of age become chronically infected [3]. Chronic infection can go undetected for decades, until the disease becomes evident and might lead to serious complications [4].

The natural history of the infection may differ according to whether the infection has occurred in early childhood or during the adulthood [5]. The healing determines the disappearance of HBV surface antigen (HBsAg)[1] proteins and the appearance of protective antibodies HBV e antigen (HBeAb): the presence of HBeAb antibodies, correlated to a low viral concentration in the blood, making the subject an "inactive carrier" of the disease. After the appearance of HBeAb antibodies and the stoppage of the disease process, two circumstances might occur:

- the subject might continue developing HBeAb antibodies, so determining the full resolution of the disease;
- the disease might remain inactive for years. However, the pressure exerted by the HBeAb production on the immune system might induce the virus to mutate and replicate itself despite the presence of HBeAg antibodies [6].

1.1 Epidemiology

Viral hepatitis is a worldwide major public-health issue. In particular, chronic viral hepatitis B and C are key risk factors for the development of cirrhosis and hepatocellular carcinoma (HCC). The World Health Organization estimated that 600,000 annual deaths are due to the complications related to chronic HBV infections. A quarter of the world's population has been infected by HBV: previous studies estimated that around 350 million people are healthy carriers of the virus [9].

In Italy, where HBV has faced a strong reduction during the last years, achieving a value of 0.9/100,000 inhabitants in 2010, healthy carriers number around half a million and the average estimated number of patients on treatment for the management of an HBV infection is around 20,000 [10].

1.2 Therapies

A pharmacological treatment for the management of the disease has the goal to eradicate/minimize the presence of HBsAg antigens: the loss of surface antigens and the possible occurrence of specific antibodies (seroconversion) is associated with a complete remission and long-term clinical favourable outcomes. Although none of the currently available drugs allows to fully defeat the infection, they reduce the replication of the virus, thus minimizing liver damage. To date, there are seven approved drugs for the treatment of HBV; these include the antiviral drugs lamivudine (Epivir), adefovir-dipivoxil (Hepsera), tenofovir (Viread), telbivudine (Sebivo), entecavir (Baraclude) and immune-system modulators, such as the interferon α-2a and the peginterferon α-2a (Pegasys). The use of interferon has been supplanted by the prolonged action of the pegylated interferon administered once a week [4].

Entecavir and tenofovir disoproxil fumarate belong to the third generation of nucleos(t)ide analogues (NAs) recommended as a fist-line treatment for patients affected by HBV. Both are characterized by high efficacy and almost no risk of developing drug resistance. Compared to interferon, the NAs not only achieve higher rates of virologic suppression, but are also characterized by a better safety and tolerability profile: this latter aspect is particularly relevant on account of the long-term use these drugs require [11–13]. The treatment based on these drugs lasts from 6 months to 1 year, depending on the genotype of the virus [14]. In patients treated with antivirals, the prolongation of the therapy increases the rates of seroconversion as well as the risk of developing a drug resistance. The persistence of the seroconversion after the end of a therapy is lower for therapies based on antivirals than those based in peginterferon [15]. According to previous studies, tenofovir is the most suitable drug for pregnant women affected by HBV [16]. In particular, the guidelines developed by the European Association for the Study of the Liver (EASL) [17] and the American Association for the Study of Liver Diseases (AASLD) [18] indicate both tenofovir and entecavir for the management of HBV

[1] "HBsAg" stands for HBV surface antigen: these antigens are recognized by proteins with antibody functions that bind specifically to one of these surface proteins. Patients who have developed antibodies against HBsAg (seroconvertion) are usually considered non-infectious. If HBeAg antibodies are found in absence of all the other markers of a HBV infection, it means that the patient has been vaccinated [7]. If HBsAg are found in the blood, this means that the virus is actively replicating and the patient is infectious [8].

infections without providing a clear guidance on the choice between them, unless specific categories of patients are taken into account, such as pregnant women and patients characterised by resistance to previous therapies.

In view of the above, this analysis seeks to compare the cost effectiveness and budget impact of entecavir and tenofovir as first-line therapies for the treatment of patients with HBV infections in Italy.

2 Methods

2.1 Model Description

The analysis was realised by building a Markov model based on the natural history of the disease entailing six health states [19], in order to assess the cost effectiveness of both the drugs, identified as first-line treatments by the international guidelines, as compared to the "no treatment" option and to each other (Fig. 1). The model was developed by ALTEMS, School of Health Economics and Management at Catholic University of Sacred Heart, Rome, Italy: two researchers (MB and MR) developed a model independently of each other and a third researcher (SC) performed a comparison in order to check the goodness of the results achieved. The model considered a hypothetical sample of 1000 naïve-treatment individuals affected by HBV, the perspective of the Italian NHS and a life-time horizon. As the optimal length of the treatment is unknown and the chronic infection implies the chance to eradicate the virus by its own within 6 months, the cycle of the model was set to the longer period of 1 year to compare the level of expenditures and patient utility between the scenario concerning the natural history of the disease through the years (no treatment) and that considering the administration of a therapy based either on entecavir or tenofovir. At every cycle the patient may either remain in the state he/she was classified with the year before, starting from chronic HBV, or progress to a less desirable health state: compensated cirrhosis (CC), decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC), but cannot move backward. When the patient reaches the "decompensated cirrhosis" state, he/she might be at risk of a liver transplantation. No alternatives were considered for the scenario in which the patient fails to respond to one of the treatments under analysis [41].

If the treatment is effective, the patients remain in the starting state, otherwise they progress to the following stages of the disease. The model included direct costs per health state while effectiveness data were expressed in terms of QALYs (quality-adjusted life years) assuming a discount rate equal to 3.5% for both costs and benefits. Results of the model were expressed in terms of incremental cost-effectiveness ratio (ICER). Based on the previous literature on cost-effectiveness analyses realized in the Italian context [38] and in absence of a specific recommended value, we set the threshold at 30,000€/QALY in order to assess the acceptability of the treatments by the Italian Health Service.

Furthermore, the study developed a budget impact (BI) model entailing the computation of the costs related to the provision of the two treatments as compared to the scenario considering only the natural history of the disease, able to provide clinicians and decision makers with a guidance to consider when selecting a therapeutic approach based on the principles of the good clinical practice in the Italian context [17].

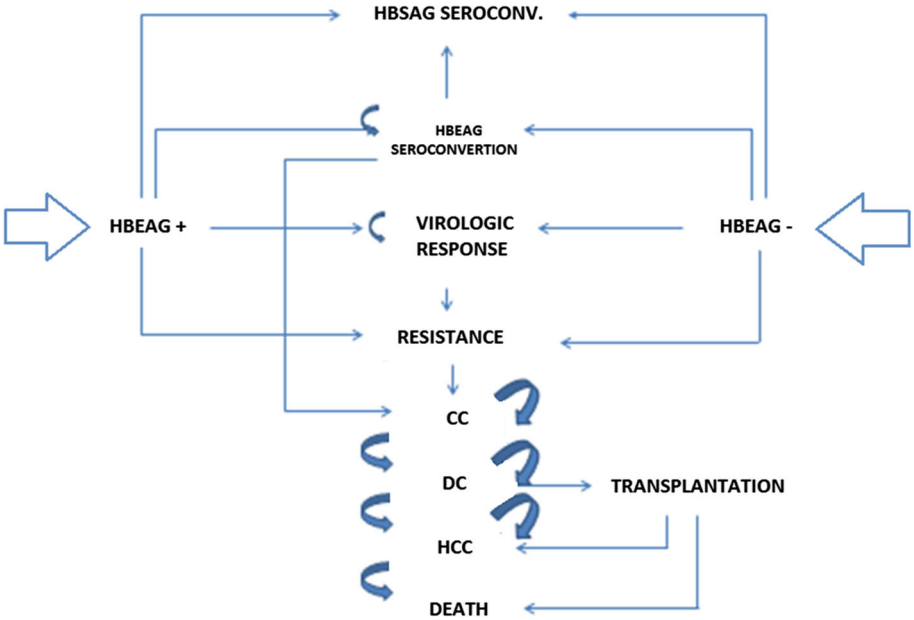

Fig. 1 Markov model representation. *HBV* hepatitis B virus infection; *CC* compensated cirrhosis; *DC* decompensated cirrhosis; *HCC* hepatocellular carcinoma; *SEROCONV* seroconversion; *HBEAG* hepatitis B e-antigen

Seeking to obtain accurate details about the therapeutic path of tenofovir, the researchers referred to the Italian medical division of Gilead Sciences Inc. as maximum exponent of the characteristics of the product. All data included in the analysis were obtained by interrogating a panel of expert clinicians suggested by Gilead Sciences Inc., gathered in a Scientific-Technical Committee (STC) through the administration of a questionnaire in order to compare the clinical practice of several health structures. The STC was composed of three expert haematologists from three Italian health structures (one from the North, one from the Centre and one from the South) who also took part in a preliminary board meeting where the main parameters related to the therapy as well as the sources of clinical data to be included in the model were identified. Therefore, despite that the clinicians were suggested by Gilead Sciences Inc., their participation was limited to the definition of the general provision process of the therapy: frequency and duration of visits, exams, checks the patients face during the treatment, the resources used, etc. At the end of the research programme the clinicians, together with the researchers, validated the correctness of the study: the combined panel checked for face validity (the panel evaluated model structure, data sources, assumptions, and results), internal validity (accuracy of coding), cross validity (comparison of results with other models) and external validity (comparing model results with real-world results).

2.2 Parameters of the Model

Transition rates of moving from a given health state to another according to the natural history of the disease were extrapolated from the literature [19–25]. Table 1 shows the average values of all the transition rates considered in the model, whose alpha and beta parameters necessary for the realization of the sensitivity analyses were derived from their standard deviations assuming a random Beta-distribution (see "Appendix").

2.3 Estimated Efficacy Data

Efficacy data calculated on a 5-year time horizon for positive and negative HBeAg patients are reported below (Table 2). In particular, we considered the rates of virologic response, the rates of resistance to the treatment, and the rates of clearance and seroconversion. Data concerning the effectiveness of the two drugs in inducing patients' virologic response were used to adjust the transition rates, referred to the natural history of the disease in order to reflect their impact on the likelihood of a worsening of the health conditions. The values reported in Table 2 were applied to the health states not included in the natural history of the disease (reported in Table 1). Because the drugs are characterised by different values in terms of virologic response, resistance and seroconversion rates, patients flowed differently among the health states included in the model according to the drug used.

Table 1 Transition probabilities

Transitions	Average	SD	References
CC to DC	0.0340	0.0071	[21]
CC to HCC	0.0435	0.0417	[24]
DC to HCC	0.0435	0.0417	[24]
DC to transplant	0.0310	N/A	[25]
DC to death	0.1410	0.0170	[24]
HCC to death	0.3105	0.1648	[24]
Transplant to death	0.2275	0.0559	[22]
HBV to CC	0.0690	0.0057	[25]
HBV to HCC	0.0140	N/A	[24]

HBV chronic hepatitis, *CC* compensated cirrhosis, *DC* decompensated cirrhosis, *HCC* hepatocellular carcinoma

2.4 Consumption and Valuation of the Economic Resources

Costs related to hospitalization, outpatient visits and diagnostic exams were valued according to the Italian NHS perspective and referred to the year 2014, while the enhancement of the costs related to both treatments was realised according to the National Pharmaceutical Handbook [25]. The cost related to specialist visits and diagnostic tests was calculated by applying the rates of the "Nomenclatore Tariffario delle Prestazioni Specialistiche Ambulatoriali" [26]. Because the services are provided on an outpatient basis, we considered the abdomen echography (88.76.1) and esophagogastroduodenoscopy (43.41.3), whereas we evaluated hospital admissions for cirrhosis, hepatocellular carcinoma and liver transplantation by using the corresponding DRG (diagnosis-related group) tariff.[2]

Regarding the admissions to the HCC health state, we used the average cost of DRGs 199 (diagnostic procedures for hepatobiliary malignancies), 201 (other hepatobiliary interventions or interventions on the pancreas) and 203 (malignancies interesting the hepatobiliary apparatus or the pancreas) while we used the DRG 480 as a reference to compute the cost of a liver transplantation. Table 3 shows the average value and the standard deviation referred to the yearly consumption of resources per patient in relation to

[2] In particular, as to the hospitalizations related to decompensated cirrhosis, average prices of the following DRG were considered: 191 (operations on pancreas, liver and shunt with DC), 192 (operations on pancreas, liver and shunt without CC) and 200 (hepatobiliary diagnostic procedures).

Table 2 Efficacy data

	Year 1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	References
Virologic response rates—positive HBEAG patients						
Tenofovir	76	78	71	77	65	[32–34]
Entecavir	67	80	82	91	94	[17, 35]
Virologic response rates—negative HBEAG patients						
Tenofovir	93	91	87	86	83	[32, 33, 36]
Entecavir	90	94	93	91	95	[19, 37]
Resistance rates—positive HBEAG patients						
Tenofovir	0.00	0.00	0.00	0.00	0.00	[13, 32, 33, 38]
Entecavir	0.20	0.50	1.20	1.20	1.20	[12, 17, 39]
Resistance rates—negative HBEAG patients						
Tenofovir	0.00	0.00	0.00	0.00	0.00	[12, 32, 33, 38]
Entecavir	0.00	0.00	0.00	0.00	0.00	–
Clearance and HBSAG seroconversion—positive HBEAG patients						
Tenofovir	3.20	6.00	8.00	10.00	9.00	[32, 33]
Entecavir	2.00	2.00	2.00	2.00	1.4	[40]
Clearance and HBSAG seroconversion—negative HBEAG patients						
Tenofovir	0.00	0.00	0.00	0.00	0.00	[32, 33]
Entecavir	0.00[b]	0.00	0.00[a]	0.00[a]	0.00[a]	[19]
HBEAG seroconversion—positive HBEAG patients						
Tenofovir	21.00	26.00	26.00	31.00	40.00	[32, 33]
Entecavir	21.00	31.00	31.00[a]	16.00	23.00	[17, 35]

HBEAG hepatitis B e-antigen, *HBSAG* hepatitis B surface antigen

[a] Not available data, assumed to be equal to the previous year

[b] Assumption

Table 3 Resources consumption

Health states	Cost items	Yearly average/patient	SD
HBV	Hematologic visit	2.50	0.81
	Laboratory exams (HBV-DNA, CBC, liver function, protein electrophoresis)	2.50	0.81
	Abdominal echography	0.75	0.41
CC	Blood tests (alpha fetoprotein)	2.00	0.00
	Visit	2.50	0.81
	EGDS	1.50	0.81
	Abdomen ultrasonography	2.50	0.81
DC (extra-admission)	EGDS	1.50	0.81
DC (hospitalisation)	Paracentesis + albumin	N/A	N/A
HBV-	HBV-DNA	0.75	0.41
Normal transaminases	Abdomen ultrasound	0.40	0.17
HCC -hospitalisation	DRG average 199; 201; 203	N/A	N/A
HCC follow-up	Alpha FP; abdomen echography	2.00	N/A

HCC hepatocellular carcinoma, *HBV* hepatitis B virus, *DC* decompensated cirrhosis, *CC* compensated cirrhosis, *EGDS* esophagogastroduodenoscopy

the gravity of the disease. To perform a sensitivity analysis, a Beta-distribution was applied to the mean values of each cost driver included in the model, using alfa and beta values to calculate the standard deviation referred to each item (see "Appendix").

Table 4 shows annual direct costs related to the different health states considered in the model. Healthcare costs for examinations and visits amount to €318.86 for patient affected by chronic HBV, to €602.34 for those affected by CC. The highest expenditure of resources (excluding the

Table 4 Estimated annual direct costs per health status

Health states	Total costs (€)
Chronic hepatitis B	€318.86
Compensated cirrhosis B	€602.34
Decompensated cirrhosis B	€3354
Hepatocellular carcinoma	€4759.50
Liver transplant	€62,012
Entecavir	€4595
Tenofovir	€3062

Table 5 Estimated utility data

Health states	Average	SD
Chronic hepatitis (HBV)	0.88	0.08
Compensated cirrhosis (CC)	0.80	0.08
Decompensated cirrhosis (DC)	0.70	0.11
Hepatocellular carcinoma (HCC)	0.53	0.40
Liver transplant	0.70	0.18

liver transplantation) is associated with those affected by HCC and DC (€4759.50 and €3354, respectively). Finally, liver transplantation is the most expensive health state, with a total cost equal to €62,012.

2.5 Estimated Utility Data

Utility data were obtained by computing the mean values extracted from the available literature. In particular, we considered the utilities obtained from Sullivan [23] and Nakamura [24] as extreme values of a 95% confidence interval in order to determine the standard deviation used in the model. Factors related to the quality of life per health state were computed by using the Health Utility Index (HUI) method. In Table 5, the utilities associated to each health state are shown (full details in the "Appendix"). Standard deviations for each parameter were computed by using alfa and beta values of the Beta-distribution associated with these variables. Utility data pertaining to a German sample of patients affected by hepatitis C virus (HCV) analysed in the study by Siebert et al. [27], and applied to the case of HBV infection as both infections imply the same course of the disease. The applicability of these data to the Italian population might be considered as a limitation of the analysis.

2.6 Sensitivity Analysis

A probabilistic sensitivity analysis [28] was performed using a Monte Carlo simulation to realize a set of 1000 scenarios, obtained by making all the parameters included in the model vary simultaneously. As to the costs considered in the model, we assumed a random Gamma distribution, whereas parameters related to the efficacy were made to vary assuming a random Beta-distribution. Results from the Monte Carlo simulation were reported in a cost-effectiveness plane, allowing to perform an analysis upon their distribution of the results around the base-case. By using the results of the cost-effectiveness analysis, it was possible to derive the willingness-to-pay of the population: the cost-effectiveness acceptability curve (CEAC) shows the percentage of simulations for which the treatments resulted cost-effective, compared to the alternative in relation to increasing levels of the willingness-to-pay.

2.7 Budget Impact Analysis

The assessment of both the drugs was completed with a budget impact analysis (BIA) providing estimates of the financial impact of the consumption of resources in both the provision of the treatments and the natural history of the disease, considering a time horizon of 5, 10 and 15 years. A BIA allows to assess the financial feasibility in the short term (at a national, regional or local level) of a new health technology and should be seen as an integration of the cost-effectiveness analysis. We considered a sample population of 20,000 individuals (average number of patients yearly on treatment in Italy [10]) and costs data related to drugs, admissions and services provided. Additionally, we considered an incidence equal to 3/100,000 inhabitants and a yearly reduction of this rate equal to 4% [estimated from Emilia Romagna (Northern Italy) data].

3 Results

3.1 Base-Case Analysis

The base-case results from the comparison of tenofovir versus "no treatment" and entecavir versus "no treatment" are summarised in Table 6.

The total cost referred to the "no treatment" option was the lowest among the options considered. However, in terms of QALYs gained, the greatest efficacy was the one related to tenofovir, resulting in 19.19 QALYs, compared with 14.30 QALYs for the untreated population: incremental costs, as to the comparison against tenofovir, amounted to €50,218.90, with an incremental gain of 4.89 QALY in favour of tenofovir. Additional costs for entecavir amounted to €79,032.91, with a differential in terms of efficacy equal to 4.85 QALYs in favour of entecavir. The cost for the implementation of a therapy based on entecavir amounted to €93,365.13 and resulted in a gain of 19.15 QALYs: ICERs from the comparison of tenofovir

and entecavir versus the "untreated population" scenario amounted to €10,274.73 and €16,300.44, respectively.

Concerning a direct comparison between tenofovir and entecavir, the former allows to achieve a higher level of QALYs, with a positive differential equal to 0.04 QALYs. This increased level of effectiveness was achieved with a lower consumption of resources: tenofovir was associated with a saving of €28,814.01 in the comparison with the resources needed to provide the treatment based on entecavir. These results in terms of effectiveness and resources consumption determined a dominant ICER for tenofovir (Table 7).

3.2 Probabilistic Sensitivity Analysis

Results shown in paragraph 3.1 were used as a base-case in order to perform a probabilistic sensitivity analysis (PSA) [29], realised in order to check the robustness of the deterministic results achieved by comparing the drugs under investigation against the "no treatment" scenario. Figure 2 shows the cost-effectiveness plane referred to entecavir as compared to the "no treatment" option.

The distribution of the ICERs relative to the comparison of entecavir versus the "no treatment" option showed a gain of 0.88–16.08 QALYs in favour of entecavir and incremental costs ranging from €78,205.83 to €80,256.87. Because most of the 1000 simulations achieved considering the simultaneous variation of all the parameters included in the Monte-Carlo analysis fell below the threshold considered (30,000€/QALY), we could conclude that the treatment based on entecavir is associated to a good cost-effectiveness profile in the comparison with the "no treatment" scenario.

When analysing the comparison between tenofovir and the natural history of the disease (Fig. 3), the cost differential lay between €49,535.38 and €50,996.38, whereas the gain in terms of QALYs fell in the range 0.85–16.93. As in the previous multi-way sensitivity analysis, most of the

Table 6 Base-case results for tenofovir and entecavir versus no treatment

Treatment	Costs (€)	QALYs	Δ Costs (€)	Δ QALY	ICER (€)
No treatment	14,332.22	14.30	–	–	–
Tenofovir	64,551.12	19.19	50,218.90	4.89	10,274.73
Entecavir	€93,365.13	19.15	79,032.91	4.85	16,300.44

QALYs quality-adjusted life years, *ICER* incremental cost-effectiveness ratio

Table 7 Base-case results for tenofovir versus entecavir

Treatment	Costs (€)	QALYs	Δ Costs (€)	Δ QALY	ICER
Entecavir	93,365.13	19.15	–	–	–
Tenofovir	64,551.12	19.19	−28,814.01	0.04	Dominant

QALYs quality-adjusted life years, *ICER* incremental cost-effectiveness ratio

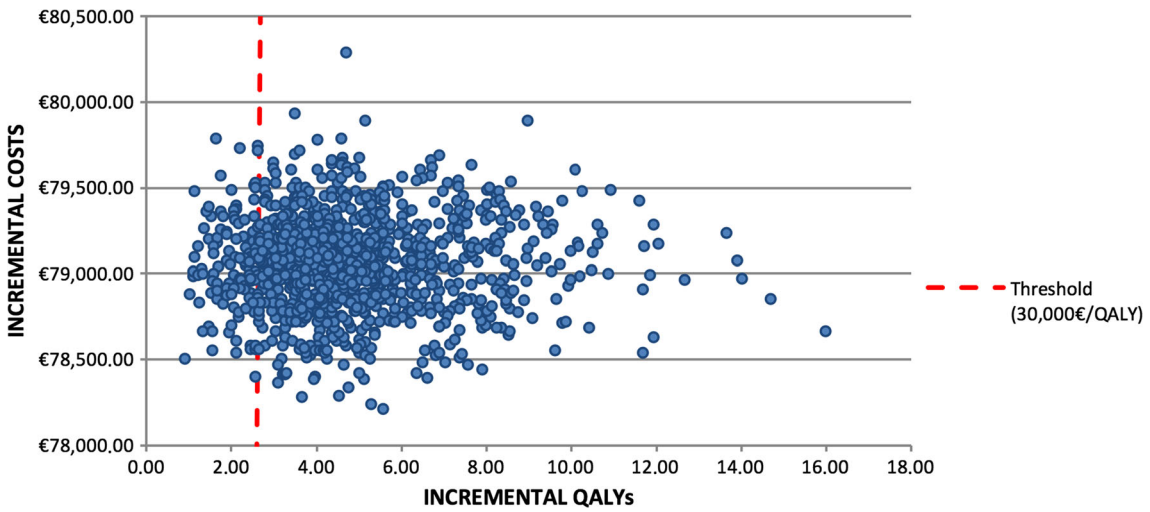

Fig. 2 Probabilistic sensitivity analysis of entecavir vs. "no treatment"

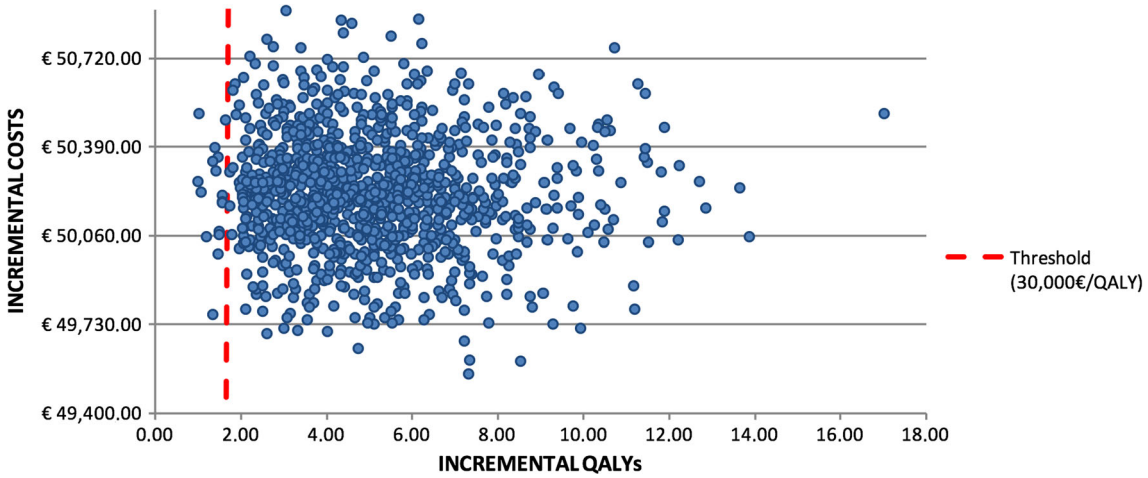

Fig. 3 Probabilistic sensitivity analysis of tenofovir vs. "no treatment"

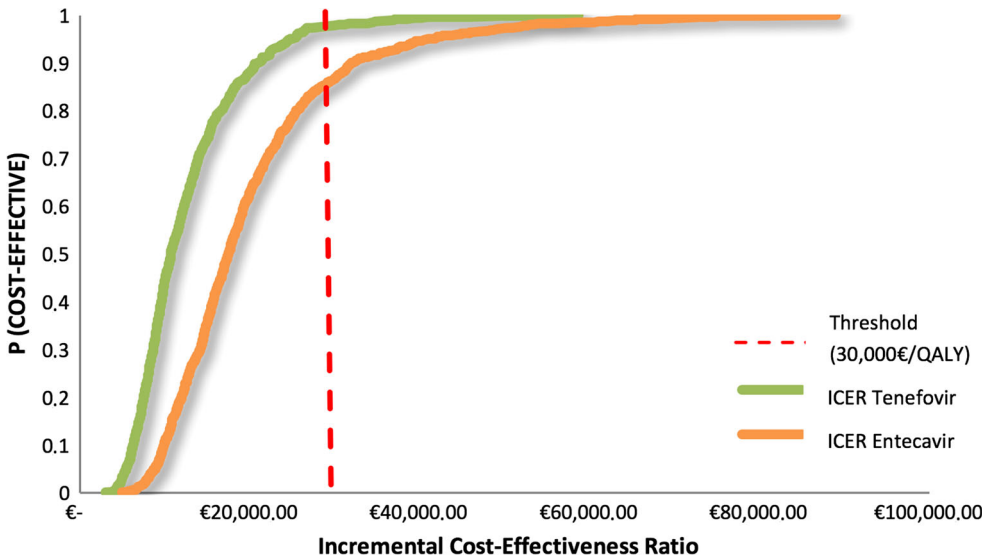

Fig. 4 Cost-effectiveness acceptability curve (CEAC)—tenofovir and entecavir vs. no treatment

1000 Monte Carlo simulations realised considering the simultaneous variation of all the parameters included in the model fell below the threshold of 30,000€/QALY, showing the cost effectiveness of tenofovir in the comparison with the "no treatment" scenario.

The result of the "no treatment" option was predictably less cost effective as compared to both the alternatives. By comparing the results derived from the cost-effectiveness planes referred to the comparisons versus the "no treatment" option, it was observed that tenofovir was the best alternative, allowing to achieve a better quality of life with a lower consumption of resources.

This evidence was highlighted by presenting the results from the Monte Carlo simulations on the CEAC. The CEAC (Fig. 4) shows the probability of being cost effective in relation to different levels of willingness-to-pay: we could conclude that the treatment based on tenofovir has the highest cost-effectiveness profile, because the likelihood of this treatment being cost effective in the comparison with the "no treatment" scenario is always higher than that of entecavir in comparison with the same alternative.

In particular, for a threshold (payer's willingness-to-pay) of 30,000€/QALY (red vertical line in Fig. 4), the likelihood of tenofovir to be cost effective was 97%, and it progressively increased for increasing levels of the threshold. As to the entecavir-based treatment, its probability of being cost effective for a threshold set to 30,000€/QALY was around 85%, and increased more slowly for increasing values of the threshold.

3.3 Budget Impact Analysis

The BIA examined the costs associated with the alternatives included in the study on a multi-horizon perspective

Table 8 Budget impact analysis (€)

Treatment	1 year	5 years	10 years	15 years
No treatment	6,667,462	10,673,403	18,645,489	24,460,699
Tenofovir	66,507,763	79,962,783	85,169,062	84,513,595
Entecavir	99,805,085	115,376,323	122,946,552	122,048,016
Tenofovir vs. no treatment	59,840,300	69,289,380	66,523,573	60,052,896
Entecavir vs. no treatment	93,137,622	104,702,920	104,301,062	97,587,317
Tenofovir vs. entecavir	−33,297,322	−35,413,540	−37,777,490	−37,534,421
Tenofovir vs. entecavir (%)	−33%	−31%	−31%	−31%

(1, 5, 10 and 15 years) in order to check the impact on the budget determined by the implementation of a therapy based on both the drugs, compared to the amount of costs associated with the "no treatment" scenario. Also, in this case, we considered a reference population of 20,000 individuals [10].

Table 8 shows the cost of each treatment as well as the incremental cost of tenofovir in comparison with entecavir. With the exception of the 15th year, in which we observed a slight decrease in the differential consumption of resources, costs of all the alternatives steadily increased over time. Comparing the absolute amount of resources associated with both the therapies, results showed a saving of 33% for tenofovir during the first year on treatment compared to entecavir and 31% during the following years.

4 Discussion

The present analysis demonstrated that both entecavir and tenofovir are significantly more effective than the "no treatment" option, with a differential in terms of QALYs of 4.89 for tenofovir, and 4.85 QALYs for entecavir. In terms of costs, as expected, both the treatments imply a higher expenditure compared to the alternative: incremental costs are equal to €50,218.90 and €79,032.91 for tenofovir and entecavir, respectively. Despite the huge difference in terms of costs, both treatments are able to substantially improve the health state of an individual affected by HVB and, therefore, they can both be considered as a first-line treatment option. The ICER of tenofovir compared to the "no treatment" option equals €10,274.73, while the ICER of entecavir amounted to €16,300.44. In both cases, ICER is below the acceptability threshold established by NICE (€25,000–€35,000) indicating the economic sustainability of both the treatments.

The robustness of the results was analysed by mean of a probabilistic sensitivity analysis. The simulations performed show a greater efficacy of both the drugs as compared to the "no treatment" option in most of the iterations, despite the positive differential in terms of costs: these results were highlighted by representing a CEAC, which demonstrated the greatest cost effectiveness of tenofovir in the management of patients affected by chronic HBV. Finally, by assessing the financial impact of the alternatives, we determined a savings of 33% associated with the use of tenofovir as compared to the therapy based on entecavir during the first year and 31% thereafter. These results are consistent with those obtained in previous reports stated at international levels [30] and by Colombo et al. [31] for Italy, where it is reported a higher cost effectiveness for both the drugs as compared to the natural history of the disease [31]; however, in this latter study the direct comparison between entecavir and tenofovir was not performed. The construction of the model used in this analysis does not allowed a direct comparison between the results obtained in this study and those achieved by Iannazzo et al. [42], as in the present analysis the researches did not include the treatment based on pegylated interferon among the comparators and could not achieve conclusions about the cost effectiveness of using this treatment for the management of patients affected by HBeAg-negative chronic hepatitis B before switching to either entecavir or tenofovir. Furthermore, this is the first published analysis realised in the Italian context exclusively comparing entecavir and tenofovir and including a BI analysis among those available in the scientific literature.

The main limitation of the study is dependent on the use of utilities and effectiveness data applied to the Italian context without accounting for the differences across populations. Several assumptions were made due to a lack of data concerning entecavir: we assumed a resistance rate for negative HBeAg patients equal to zero for the first year and constant for the following years; we assumed the clearance and the HBsAg seroconversion rate for HBeAg-positive patients stayed equal to those of the previous year when these data were not available in literature; we used the same criteria for clearance and HBsAg seroconversion data of negative HBeAg patients; and regarding the third year, we assumed the rate of HBsAg seroconversion for positive HBeAg patients being equal to the one computed for the previous year. Furthermore, the study does not consider a rescue therapy in case the patient does not respond to one of the alternatives analysed. Finally, the researchers only focused on the main two therapies (entecavir and tenofovir) and other first-line therapeutic paths were not included in the analysis.

5 Conclusions

To date, several treatments for chronic HBV are available in Italy. Today's guidelines recommend the use of both tenofovir and entecavir as first-line therapies for the treatment of chronic HBV infections. Pharmacoeconomic evaluations can aid decision-makers' choice of therapy. The results of this modelling analysis suggest that tenofovir is cost effective compared with entecavir as first-line treatment for patients suffering chronic HBV infections before they develop cirrhosis and are able to decrease the rates of morbidity and mortality associated with HBV in Italy.

Compliance with Ethical Standards

Authors contributions All authors made a substantial contribution to the conception, design, acquisition of data and related analysis and interpretation, and participated in drafting the article and revising it critically and according to its important intellectual content.

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Appendix

Transition rates	Cost items	Average	SD	Alpha	Beta
CC to CS	–	0.0340	0.0071	0.1239	3.5209
CC to HCC	–	0.0435	0.0417	0.0434	0.9539
DC to HCC	–	0.0435	0.0417	0.0434	0.9539
DC to Transplant	–	0.0310	N/A	N/A	N/A
DC to death	–	0.1410	0.017	0.8653	5.2717
HCC to death	–	0.3105	0.1648	0.0930	0.2065
Transplant to death	–	0.2275	0.0559	0.4882	1.6578
HBV to CC	–	0.0690	0.0057	0.7146	9.6414
HBV to HCC	–	0.0140	N/A	N/A	N/A
Resources consumption by health state					
HBV	Hematologic visit	2.50	0.81	16.7890	10.0734
	Laboratory exams (HBV-DNA, CBC, liver function, protein electrophoresis)	2.50	0.81	16.7890	10.0734
	Abdominal echography	0.75	0.41	0.0866	0.0289
CC	Blood tests (alpha fetoprotein)	2.00	0.00	400,000,002	200,000,001
	Visit	2.50	0.81	16.7890	10.0734
	EGDS	1.50	0.81	3.2147	1.0716
	Abdomen ultrasonography	2.50	0.81	16.7890	10.0734
DC (extra-admission)	Esophagogastroduodenoscopy (EGDS)	1.50	0.81	3.2147	1.0716
DC (hospitalisation)	Paracentesis + albumin	N/A	N/A	N/A	N/A
HBV-normal transaminases	HBV-DNA	0.75	0.41	0.0866	0.0289
	Abdomen ultrasound	0.40	0.17	2.9218	4.3827
HCC-hospitalisation	DRG Average 199; 201; 203	N/A	N/A	N/A	N/A
HCC follow-up	Alpha FP; abdomen echography	2.00	N/A	N/A	N/A
Utilities by health state					
Chronic hepatitis (CE)	–	0.88	0.085	12.02667	1.64
Compensated cirrhosis (CC)	–	0.80	0.08	20.3570	5.0893
Decompensated cirrhosis B (CS)	–	0.70	0.11	10.7844	4.6219
Hepatocellular carcinoma (HCC)	–	0.53	0.40	0.3120	0.2767
Liver transplant	–	0.70	0.18	3.6491	1.5639

In the model a Gamma distribution is used for costs, while data related to the effectiveness are assumed to vary according to a Beta distribution in order to perform the sensitivity analysis

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